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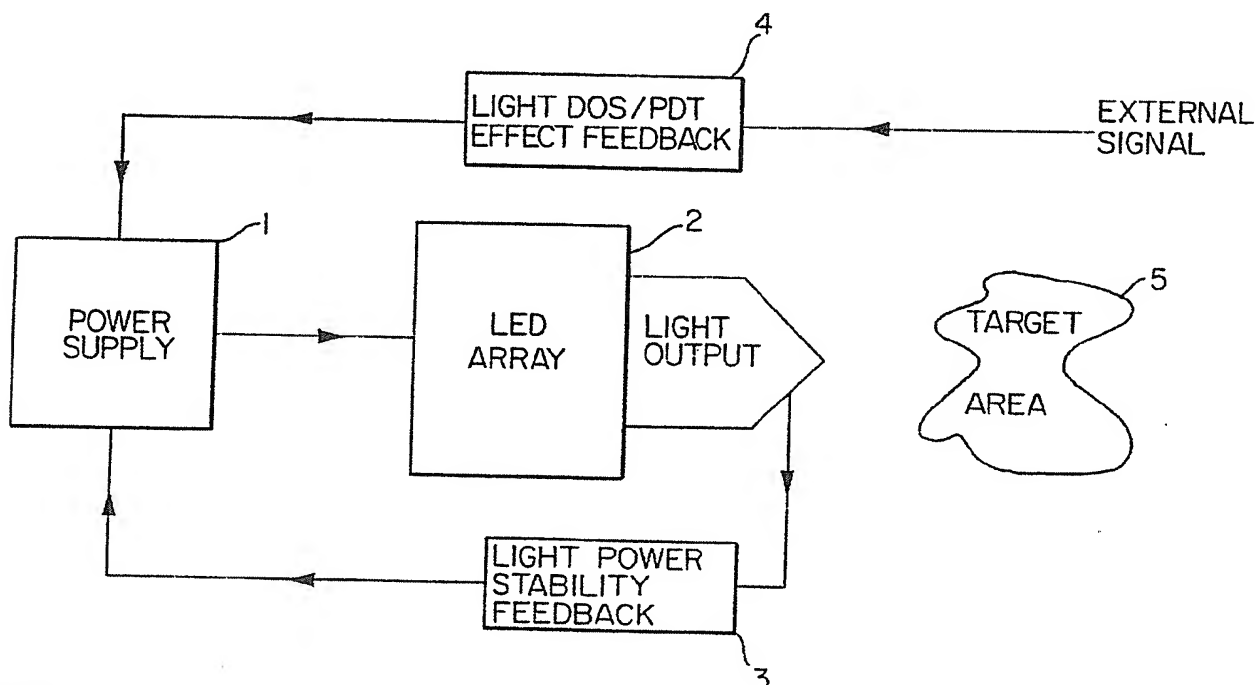
(57) Abstract

A method and system for activating photosensitizers for PDT *in vivo*, extracorporeally, and *in vitro*, where the light sources used are high-power light-emitting diodes (LEDs) and the LED wavelength band output is selected to access a given absorption band of the photosensitizer. The system includes a power supply (1), an array of LEDs (2), feedback loop (3) for monitoring LED output power and feedback loop (4) for monitoring light delivered to target area (5).

5   HIGH-POWER LIGHT-EMITTING DIODES
                       FOR PHOTODYNAMIC THERAPY

       Field of the Invention
                     The invention generally relates to the use of
10   high-power light-emitting diodes (LEDs) for use in
       photodynamic therapy (PDT). More specifically, high-
       power LEDs emitting a suitable wavelength band are used
       to activate photosensitive drugs for *in vitro*,
       extracorporeal, or *in vivo* PDT. The aim is to
15   selectively impair or destroy targeted cancerous or
       otherwise undesirable tissues or cells while leaving
       healthy tissues or cells unaffected.

       Background of the Invention
20   PDT or photodynamic therapy has become a
       recognized means of treating certain types of cancer. A
       review of many of the areas in which it has been applied
       is given by S.L. Marcus in 'Proceedings of the IEEE' (in
       publication). In essence, a photosensitizer such as
25   PHOTOFRIN® porfimer sodium or BPD (benzoporphyrin
       derivative) is administered systemically to a patient
       with cancer. The drug distributes through the body in
       such a manner that it is found in higher concentrations
       at the diseased site. This can take several hours to a
30   few days depending on the drug. A suitable light source
       is then used to activate the drug in the tissue.
                     An alternative scenario to the above would be
       one in which the drug is administered topically to the
       target tissue, e.g., a psoriatic lesion, site of viral
35   infection, wart, or port wine stain. Once again, after

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the drug has been taken up by the target site, the light
source can be directed at the target to activate the
drug, either via a fiber or by direct illumination.

Several photosensitizing compounds have been
5   tested *in vivo* as potential clinical photosensitizing
drugs, including PHOTOFRIN* and its precursor
hematoporphyrin derivative, BPD, chloroaluminum
phthalocyanine tetrasulfonate, zinc phthalocyanine
tetrasulfonate, protoporphyrin IX, purpurin, merocyanine
10   540, methylene blue, tetraphenylporphyrin sulfonate,
pheophorbide, monoaspartyl chlorin e6. These
photosensitizers are activatable by light in the 500 nm
to 780 nm range.

The mechanisms by which PDT works are complex,
15   and the activation mechanisms may differ from one
photosensitizer to another. However, a feature common to
all of these photosensitizers is that they are activated
by the absorption of light. For absorption to take
place, the wavelength of light must coincide with a
20   suitable photosensitizer absorption band. The absorption
results in energy being deposited into the
photosensitizer and subsequently initiates a series of
chemical reactions which result in the death of cells.
Since the energy is deposited only where the
25   photosensitizer is located, only cells local to the
photosensitizer are killed. The result of the cells'
death depends on the treatment being performed. For
example, in the case of photosensitizers such as
PHOTOFRIN*, where the PDT is being done to eradicate a
30   tumor, this cell killing appears to give rise to both
localized destruction of the tumor tissues and to local
vascular damage to the blood vessels supplying the tumor.
The net result for correctly applied light and
photosensitizer doses is for the tumor to be killed but
35   not the surrounding healthy tissues.

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To maximize the cell killing, the photosensitizer should have a strong absorption band, and the energy deposited into the photosensitizer should be efficiently converted into chemical reactivity. One
5   mechanism by which this is achieved is outlined here. A photosensitizer in a singlet ground state is promoted into an excited singlet electronic state by photon absorption. This absorption will tend to be strong since it is a fully allowed transition. The excited singlet
10   state will have a radiative lifetime on the order of a few nanoseconds. Vibrational relaxation within the excited singlet state to the lowest vibrational levels is rapid (10^{12} s^{-1}). The excited singlet state can emit a photon, undergo a spin-allowed internal conversion to the
15   ground singlet state, undergo a spin-forbidden intersystem crossing into a triplet state, react, or transfer its energy to another molecule. By considering the electronic state's geometry and energy separation, the reactivity of the state, the effectiveness of
20   potential quenchers and the spin orbit coupling between the singlet and triplet states, a photosensitizer is chosen such that significant production of the triplet state occurs. The triplet state will then vibrationally relax to the minimum energy of the triplet state. If the
25   triplet state is of lower energy than the excited singlet state, the triplet state will not execute an intersystem cross-back into the excited singlet state. If there is large energy gap between the ground singlet state and the triplet state, then intersystem crossing from the triplet
30   state into the ground state is typically slow. Since a triplet-to-singlet radiative transition is spin-forbidden, phosphorescence will not be a major loss mechanism. Therefore, the light energy is stored in the photosensitizer's metastable triplet state.

35

There are three major deactivation mechanisms
for this triplet state: internal conversion into the
ground singlet state, reaction of the triplet state, and
energy transfer from the triplet state. If internal
conversion into the ground state occurs, then the
metastable triplet's energy is converted into energy in
the singlet ground state. If vibrational relaxation in
the ground state is fast, then the result is localized
heating. This heating may kill cells by thermal effects.
If the singlet state's energy is greater than bond-
dissociation energy, then dissociation of the
photosensitizer may occur resulting in the formation of
radicals or radical ions, both of which may initiate
chemical reactions resulting in the localized killing of
cells. The second possibility is that the excited
triplet state reacts. Either or both of these reactions
may cause cell death. The third mechanism is energy
transfer from the excited triplet state to some other
molecule, which then initiates a chemical reaction. A
molecule which is frequently the receptor of triplet
energy is oxygen. Ground state triplet oxygen and
triplet state photosensitizer undergo a spin-allowed
energy transfer to produce ground singlet state
photosensitizer and excited singlet oxygen. This singlet
oxygen causes oxidation reactions which kill the cell.
The distance the singlet oxygen travels in an *in vivo* or
in vitro environment is limited by how far it can diffuse
during its lifetime. Since singlet oxygen has a lifetime
of 5 μs in water, it can travel 20 μm. Therefore, the
toxic effect is very localized around the
photosensitizer. The first two mechanisms lead to
reactions often referred to as Type 1, while the third
mechanism produces reactions of Type 2. A schematic of
these two reactions is shown in Figure 1. If the
photosensitizer dissociates or reacts, the

photosensitizer is destroyed and cannot participate
further in the destruction of cells. However, if the
cell-killing mechanism is primarily due to localized
thermal or energy transfer, then the photosensitizer is
5 returned to the ground state, from which it can absorb
another photon. Thus, a single photosensitizer molecule
can produce a large number of singlet oxygen molecules.
It is generally believed that the Type 2 reaction with
oxygen is the dominant reaction in PDT.
10   To be effective for PDT, the light source must
satisfy several requirements. It must emit a suitable
wavelength or band of wavelengths for activating the
photosensitizer. It should be focusable into a fiber
optic for PDT that requires a precise geometry of
15 illumination (e.g., spherical or cylindrical), or for PDT
performed in areas that cannot be directly illuminated by
the light source (e.g., endoscopic procedures - lung,
esophagus, bladder). In addition it should have an
output power high enough to ensure that the required
20 light dose can be delivered to the patient in a
reasonable time. It also should have a suitable pulsed
or continuous wave (cw) characteristic, so that the light
interacts effectively with the drug and does not damage
healthy tissues or the optic that transmit or reflect the
25 light.
         In the case of the last requirement, if the
light is emitted as a series of pulses (e.g., pulsed
laser source), then the high peak power associated with a
single pulse can damage tissue or fiber optic by a number
30 of mechanisms. These mechanisms include ablation,
thermal effects and acoustic shock waves. Similarly, if
the cw power is too high, then direct damage to the
tissue can result such as dehydration and charring. A
more complete discussion of various aspects of these
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mechanisms is given in the 'Proceedings of "Laser-Tissue Interaction" Conference', SPIE, Vol. 1202 (1990).

In general, average laser powers of a few watts are used, the maximum power being limited by existing
5   sources of high-power lasers that operate at the correct wavelengths. Where pulsed lasers are used, they are usually systems of high pulse repetition rate (1 kHz or higher), with a low output energy/shot (about 1 mJ).

It is the power density (intensity) of the
10   light that determines the effect of the light on the targeted tissue. Power densities of 10-200 mW/cm^2 are typically used for PDT. These are too low to significantly heat up the tissue, but are adequate to activate the photosensitizer, producing the desired
15   effect in a time that is short enough for clinical treatment, this typically being less than 1 hour or so.

By "clinical treatment" we refer to the actual procedure of bringing a patient who has been given the photosensitizing drug into an operating room and
20   delivering the required light dose to the target tissue. As the light dose is calculated using

$$\text{Light Dose } (J/cm^2) = \text{Power Density } (W/cm^2) \times \text{Time (s)},$$

25   it is clear that if 100 J/cm^2 is needed to activate the drug and produce a "cure," then the time required to do this is determined by the power density available from the light source: e.g., if only 1 mW/cm^2 is available, then 100,000 seconds, or 27 hours 46 minutes, are needed.
30   If 150 mW/cm^2 is available, then only 11 minutes 7 seconds are needed. In terms of patient comfort and physician and operating room time, the high power densities that lead to shorter treatment times are obviously desirable.

35

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These power density requirements also limit the maximum area that can be treated by existing lasers. Typically around 1-4 W of power is available from a laser. The maximum area that can be treated is defined
5   by

$$Area \ (cm^2) = Power \ (W) \div Power \ Density \ (W/cm^2),$$

which gives an area of 27 cm^2, assuming that 4 W at 150
10   mW/cm^2 was used. Some procedures require much larger areas than 27 cm^2 to be treated. At present these can only be done with multiple treatments, each treatment step being at a new location. With a higher power light source, larger areas could be treated with a single
15   treatment.

Until now the only light sources that have satisfied all of the PDT criteria given above were large laser systems, such as argon-ion pumped-dye lasers, copper vapor pumped-dye lasers, gold vapor lasers,
20   excimer pumped-dye lasers, and the so-called KTP pumped-dye lasers.

Patented examples of specific lasers being used for PDT may be found in U.S. Patent 4,336,809 to Clark, which discloses a xenon-ion laser, and U.S. Patent
25   4,614,190 to Stanco et al., which discloses a pulsed-laser photoradiation scheme. Both of these are complex gas-laser-based technologies. Many other practical examples of these and other lasers being used in clinical procedures exist within the scientific and medical
30   literature.

A number of ingenious non-laser sources have also been developed that partially fulfil the requirements, but they are only suitable for treatment of small lesions and are limited in the power they can
35   provide to a fiber system for endoscopic applications.

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U.S. Patent 4,757,431 to CROSS discloses the use of off-axis concave spherical reflectors as condensing and collecting optics to couple the optical output of a xenon arc lamp efficiently into a single fiber. U.S. Patent

5 4,860,172 to Schlager et al. discloses the use of a tapered coupling cone to concentrate the focused optical output of an arc lamp that is mounted in a parabolic reflector, so enabling higher optical powers to be coupled into a fiber.

10   While the laser has revolutionized PDT, the existing large-frame technology has a number of disadvantages that can be summarized as follows. The devices are physically very large. They have a poor wall-plug efficiency, where this is defined with respect

15 to the electrical power input relative to the laser power output. This results in a requirement for substantial electrical power needs and special main supply outlets rather than the normal house wall-plug socket. They require water or air cooling. They are not very

20 portable. They require periodic realignment by a trained engineer. They require a warm-up time before use and a cool-down time after use. They are very expensive and have substantial maintenance costs. They are limited in the total power they can output in the wavelength range

25 of interest.

           Light-emitting diodes (LEDs) are available that operate in the red and near infrared with power outputs up to several milliwatts/LED, they typically being continuous wave (cw), not pulsed. When the LEDs are

30 combined into a suitable array, then power densities up to 200 mW/cm^2 can be obtained. This power density is equivalent to that now being provided by lasers in PDT. Depending on the wavelength required, a variety of possible semiconductor material structures are possible.

35 Examples include AlGaAs and GaInP/AlGaInP, which can be

designed to access wavelengths in the 600-900 nm range by
carefully adjusting the parameters used to make the
device. One such method is to fine-tune the ratio of the
constituents in $Al_xGa_{1-x}As$ to produce the desired

5   results. LEDs at a variety of wavelengths are available
from commercial suppliers and are described in company
literature, e.g, Hewlett-Packard, Toshiba and Sony.

            There is only one previously reported use of
this type of technology in PDT. U.S. Patent 4,822,335 to

10   KAWAI et al. reports the use of low-power photodiodes
(where these can be laser diodes or LEDs) in a
biostimulative form of PDT. The '335 patent describes
the use of two distinct wavelength photodiodes (630 nm
and 690 nm) that, when used together, activate the

15   photosensitizer HPD (hematoporphyrin derivative) in a
synergistic manner to get the desired result. This dual
wavelength excitation was believed to access a specific
excitation route of the photosensitizer, this being
630 nm excitation to the singlet excited electronic

20   state, followed by the radiationless formation of a
triplet excited state, at which point a 690 nm photon
would excite the photosensitizer into a higher triplet
excited state prior to the usual Type 1 and Type 2
reactions that have been described earlier. At the low

25   power levels the inventors used, they achieved incomplete
activation of the drug, and minimal cytotoxicity was
observed after 48 hours. They advocate using arrays of
photodiodes to treat the target tissues, whereby these
arrays would be made up of equal numbers of the two types

30   of photodiode required. The long durations required to
kill the target cells with the method advocated by Kawai
et al. would not be suitable for any clinical treatment.

            It is the intention of the present inventors to
demonstrate the effectiveness of higher power LEDs

35   emitting a single wavelength band for PDT, so

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demonstrating their ability to overcome all of the problems described above that apply to conventional laser technologies when used for PDT of skin and mucosal tissues and in extracorporeal and intraoperative
5   applications.

Summary of the Invention

The invention comprises high-power LED systems that use a single wavelength band to photoactivate the
10   drug within a clinically acceptable time of an hour or so. The wavelength band is centered around a suitable absorption band of the photosensitizer. The LEDs are configured into arrays that permit PDT treatment of skin and mucosal tissues, and extracorporeal, *in vitro*, and
15   intraoperative applications, e.g., psoriasis, papilloma virus, port wine stains, bone marrow purging, ovarian cancer surgery. None of these applications require the light to be delivered to the target area by a fiber optic system because they can all be directly illuminated by a
20   suitably positioned LED array. The most important requirement for these applications is the ability to perform PDT over the entire area, which can be large, within a period of time that is clinically acceptable for the procedure being performed.
25   A multiplicity of LEDs can be assembled into a system with their optical power adding together to produce a combined power output that is suitable for PDT over large areas. The maximum power attained is limited only by the number of LEDs that are combined in the
30   particular system. As the LEDs are normally connected in arrays, it is the cumulative power density that is normally measured rather than the power of a single LED; i.e., over an array surface the LEDs are configured to produce the power density needed for the particular
35   treatment.

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Using large-area LED arrays would permit scaling of some of the existing PDT procedures which currently are limited by the powers available from conventional laser sources. For example, in a typical

5   dermatological procedure, light intensities of 150 mW/cm^2 are used. At 690 nm the maximum power readily available from a 20 W argon ion-pumped dye laser is 1.5-3.0 W, so limiting the treatment area to 10-20 cm^2. With multiplexed LEDs, areas of thousands of square

10   centimeters can be treated simply by adding more LEDs to the array.

The LEDs can be specifically engineered to produce the desired wavelength output for activating almost any photosensitive drug. Current examples of

15   photosensitizing drugs include PHOTOFRIN® which is activated at around 630 nm, BPD at around 690 nm, and the phthalocyanines and purpurins in the 650-680 nm range. All of these drugs have fairly broad absorption bands, so an ultranarrow laser bandwidth source is not necessary to

20   activate the photosensitizer. It is this broad absorption band that permits LEDs to be used as a replacement for the more conventional laser source, because although LEDs typically have a bandwidth of 20-30 nm, the optical power within this bandwidth is able to

25   interact with the photosensitizer.

LEDs are ideal for PDT as they can be made into compact systems and so can be truly transportable. They have very high wall-plug efficiencies (generally >10% in comparison to the more typical 1% or less of conventional

30   lasers) and so can be powered directly from a standard wall-plug socket rather than a special high power supply. They require little or no air or water cooling. They can be used immediately after being switched on and can be switched off with no major cool-down cycle. LEDs are

35   mass-producible, can be made into a compact integrated

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package, and are cheap. They require no maintenance, and
so systems assembled from them have little or no
maintenance costs. Power feedback and wavelength
monitoring can be built into a system to ensure that the
5   optical parameters do not change during the treatment,
this being very important if the correct light dose is to
be delivered.

From a practical point of view, LEDs have a
number of other advantages. They operate at low voltages
10   of about 2 V, so they can be packaged into systems that
are powered from a wall socket or a battery pack. These
low voltages also simplify compliance with electrical
safety and medical requirements: they can be easily
carried or wheeled around on a small trolley, or
15   assembled into shapes or sizes appropriate for
specialized applications. The monolithic structure of
the LEDs makes it simple to design systems that can
satisfy the requirements for sterility in a hospital
environment. It is possible to connect LEDs together in
20   a variety of ways so that the voltage-current
requirements are tailored to the electrical power supply
that is available.

Other features and advantages of the invention
will be pointed out below, or will become apparent from
25   the drawings, specification and claims that follow.

Description of the Drawings

Figure 1 is a schematic of the Type 1 and
Type 2 photochemical reactions of photosensitizers.
30   Figure 2 is an absorption spectrum of BPD in
ethanol, showing the typical broad absorption band in the
red, around 690 nm, as well as the extended absorption
down into shorter wavelengths. Also, the absorption of
oxyhemoglobin is superimposed showing the reduction in
35   oxyhemoglobin absorption as longer wavelengths in the red

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are used, i.e., as more light penetrates the tissue to interact with the drug. The y-axis denotes the molar extinction coefficients.

5   Figure 3 is a typical emission spectrum of a Hewlett-Packard LED centered at 694 nm with a full-width half-maximum (FWHM) bandwidth of 25 nm.

Figure 4 is a block diagram of the overall system concept.

Figure 5 is a block diagram illustrating ways
10   in which LEDs can be connected up so that their optical powers add to give a single broad-area light output with a predictable light intensity: (a) shows overlapping beams from each LED, (b) shows simple rows of LEDs all equally spaced, (c) shows the doubling of power density
15   available from (b) that can be achieved by inserting additional rows of LEDs.

Figure 6 shows the change in the central wavelength of light emission from 690 nm LEDs as the operating temperature of the system is changed.

20   Figure 7 shows the change in the system temperature of an array of LEDs mounted on a board as the input electrical power is increased.

Figure 8 shows the shift in the central wavelength of the LEDs as the input electrical current is
25   increased.

Figure 9 shows the shift in wavelength of the overall spectrum of light emission from the LEDs and the associated increase in light intensity as the electrical current input is increased.

30   Figure 10 shows the change in light intensity output when electrical current input is varied.

Figure 11 shows the change in power density with increasing distance from a 3.5 cm x 3.5 cm array.

Figure 12 shows the uniformity of light
35   intensity from a 3.5 cm x 3.5 cm area array.

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Figure 13 shows a typical geometry of LEDs incorporating a lens (Hewlett-Packard data sheet, type T1).

Figure 14 shows how the LEDs can be
5   incorporated into specific geometries for treating an entire person, part of that person, or a sample area of the tissue or cells of interest.

Figure 15 shows results of the *in vitro* cytotoxic dose response (MTT assay), with the percent
10   killed or impaired being compared to the controls (0.0 μg BPD), for a LED array and the argon ion-pumped dye laser (APDL).

Figure 16 is an *in vivo* equivalency study showing the percentage of animals tumor-free from day 0
15   and day 20 after exposure to the APDL and the LED array; a fixed light dose of 150 J/cm^2 and a BPD-MA drug dose of 2 mg/kg were used for all the animals.

Modes of Carrying Out the Invention/Description of
20   Preferred Embodiments

The LEDs will be chosen such that they efficiently and specifically activate the desired photosensitizer. For example, in the case of PHOTOFRIN*, wavelengths in the range of 630 ± 30 nm would be
25   suitable. In the case of BPD, wavelengths in the range of 690 ± 30 nm would be suitable. An excitation wavelength can be generalized in this way and still be effective in activating the photosensitizers because their absorption bands are fairly broad, those for BPD
30   being shown in Figure 2. The BPD absorption band at 690 nm can be compared to that of a typical 690 nm LED source that is shown in Figure 3. These LEDs are based on a transparent substrate AlGaAs material, and are obtained from Hewlett-Packard (product type T1 TS AlGaAs
35   690 nm). The FWHM of the LED spectrum is about 25 nm,

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this being similar to that of the 690 nm BPD absorption
band.

Where there is some choice between absorption
bands that can be accessed by a LED, the one used will be
5   determined by the treatment being performed. In general,
maximum penetration of light into the tissue to be
treated is required, and this necessitates the use of
longer wavelengths in the red and near infrared.
However, under circumstances where there is a specific
10   requirement to treat to a well-defined depth, then a
shorter wavelength of light can be used to activate the
drug, thus limiting the depth of light penetration.

Various types of photosensitizers can be used
in conjunction with this technology, including PHOTOFRIN*
15   and BPD, which can be obtained from Quadra Logic
Technologies, Inc., Vancouver, B.C., Canada.

Figure 4 shows some of the desired features in
the LED system. Power source 1 can be either an AC-to-
DC supply or a battery source. The LEDs can be designed
20   into the system in such a way that they can be disposed
of either with the system, or as a disposable component
that is replaced by a new plug-in LED module 2.
Typically, this type of LED has a life of over 10,000
hours, although this is a strong function of the
25   electrical current and cooling. If another wavelength is
needed to activate the particular photosensitizer in use,
then another LED module 2 with a suitable wavelength
output can be connected.

Feedback loop 3 monitors the LED power output
30   via photodiode detectors (output light power is sampled)
and via the electrical current being supplied to the LED.
The signal detected by either of these methods can be
used to stabilize the LED light power output by comparing
it to previously set reference levels and adjusting the
35

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electrical power input to compensate for any changes detected.

A second feedback loop 4 can be connected to an external dosimetry system that monitors either the light
5   actually delivered to the tissue or the real-time phototherapeutic effect at the target 5, cutting off the light output when the desired light dose or effect has been achieved.

The LED light output can be cut off during or
10   after treatment simply by cutting the electrical power. This cannot be done with the existing mainframe lasers; a shutter system must be used. A low power output can be easily obtained for alignment purposes prior to treatment either by having a preset low electrical power input or a
15   variable input power supply.

Other features that are incorporated into existing PDT light sources that aid the user of the device can also be used with LEDs. Examples of these include built-in timers used to calculate the light dose
20   delivered, green LEDs or backlit LCD displays that can be read even while wearing laser safety goggles (the goggles filter out the red display panel figures).

While it is preferred that the output should be cw, this is not an essential requirement, and a LED array
25   that is pulsed will work provided that its pulse characteristics are suitable for activating the drug and its average power is high enough.

In existing clinical trials the areas that can be treated are limited by the power available from the
30   laser. With LEDs the area that can be treated is limited only by the number of LEDs that can be connected together in the system and the power supply available. Figure 5 illustrates how the LEDs are connected together to form an array with the output of all the elements adding
35   together. A uniform power density is obtained in the

center of the array, with the power density dropping off
as the edges of the array are reached and passed, this
being shown in more detail in Figure 13.

5   The packing density of the LEDs in the array is
also critical in determining the power density that can
be obtained from it. This can be understood very easily
if one considers that if each LED has a fixed power
output of, for example, 5 mW, the number of LEDs/cm^2
multiplied by this power output will determine the power
10   density in mW/cm^2. As the number of LEDs/unit area is
increased, the maximum power density that can be obtained
from the array increases proportionately; a method by
which this is done is shown in Figures 5(b) and 5(c).
The physical size of each LED in its mounting and the
15   problems of removing the heat from the LED array
ultimately limit the maximum packing density that can be
used. In Figure 5(a), 11 refers to the circuit board of
PCB to which the LEDs are connected, 12 refers to the
individual LEDs, and 13 is the region in which their
20   beams overlap.

There are a number of factors that have to be
carefully considered in setting the power and wavelength
characteristics of the LEDs. Figure 6 shows the shift in
the central wavelength of the LEDs as the temperature
25   changes, this being about 0.25 nm/°C for these LEDs.
This means that careful control of the LEDs' temperature
can fine-tune the central wavelength of the light output.

In practice, a temperature change is also seen
as the electrical power input to the LEDs is changed,
30   assuming a fixed rate of cooling. Figure 7 shows how the
LED temperature changed as the electrical power input was
increased under these conditions. This can also be
observed in Figure 8, which shows the wavelength shift
with input electrical current to the LEDs. The overall
35   effect of increasing the input electrical current can be

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seen in Figure 9. As the electrical current is
increased, the power output of the LEDs increases, and
the emitted wavelength band shifts to longer wavelengths.

Figure 10 shows the change in power density

5   measured 2 cm in front of an array as the electrical
current into the array is increased. This demonstrates
that the optical power in the range of 0-200 mW/cm^2 can
readily be obtained with a suitably designed array.

Figures 5 to 10 illustrate that with judicious

10 use of cooling (for example, using forced air or water)
and careful selection of the operating electrical current
for a fixed LED packing density, the central wavelength
of the wavelength band from the LEDs can be set to
coincide with an absorption peak of a photosensitizer

15 while operating at a predetermined power output. In
general, the above parameters would be preset during
manufacture for the particular device in question, so
that the hospital operator would not have to make
adjustments to the device once it was installed.

20 The change in power density as one goes farther
away from an array is shown in Figure 11, where this
array is 3.5 cm x 3.5 cm. This shows that the light
intensity drops fairly rapidly as the distance increases.
Figure 12 demonstrates the good light power density

25 uniformity that is obtained with such arrays, where the
center of the array of Figure 11 is located at x=5 cm and
y=6.5 cm. All the measurements of light power density
seen in these figures are taken using a small diameter
spherical diffuser fiber (from Quadra Logic Technologies,

30 Inc.), where the diffusing sphere at the distal end
samples the light density at a given point above the LED
array. The portion of light captured by the fiber is
then transmitted to the proximal end where a calibrated
photodiode that takes into account the optical

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transmission of the fiber detector system is used to
determine the light density at that point.

Figure 13 shows a typical LED (the one used to
collect the data for this patent) that is available from
5   Hewlett-Packard. This design incorporates a lens so that
the light is emitted as a beam with a solid angle of
about 0.6 steradians.

Several arrays of LEDs can be connected
together permitting a single area equal to their combined
10   areas to be treated. Figures 14a through 14c show
examples of a number of geometries that the LEDs can be
configured into, some of which take advantage of this
ability to combine a number of panels together. Figure
14a illustrates the use of LEDs mounted to form an array
15   on a flexible or folded circuit board. The numbering
here denotes: the LEDs 21 mounted on the circuit boards
22, and the emitted light 23 incident on the target 24.
As is shown here, this could be used to treat localized
tissue areas with curved surfaces, e.g., the arm or leg,
20   or areas opened up for surgery.

Figure 14b shows large area panels connected to
form a box, or "entire body phototherapy system." This
system could be used to treat patients with extensive
psoriasis. In FIG. 14b two panels 27 and 28 carry light
25   emitting diodes which emit light 26 and 26, respectively,
onto target 29. If required front and back panels may
include light emitting diodes too.

Figure 14c shows the use of a simple panel of
LEDs for a localized cutaneous treatment of tissue, e.g.,
30   basal cell carcinoma or port wine stains. Light emitting
diodes 31 mounted on panel 32 emit light 33 onto the
treatment area of target 34

The way in which the LED arrays are connected
to the control unit will depend on the clinical
35   operation. One method is to have an array of LEDs,

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designed to activate a specific drug, attached via an
umbilical line to the control unit. The umbilical line
will carry power to the LEDs as well as relaying
information on their operating optical power output and
5   temperature, etc. back to the control unit. This geometry
is useful where the maximum flexibility is needed in
positioning the array because of space constrains. Note
also, that it is possible to disconnect an array and its
umbilical line from the control unit, and to substitute
10   it with a second array that has the required wavelength
output to activate a different drug or to achieve greater
or less penetration into tissue. Where space is less of a
problem the LED arrays can be connected directly to the
control unit, and again different LED panels can be
15   substituted in as different wavelengths are needed to
activate different drugs, or achieve greater or less
penetration of light into tissue.

        The following are examples of the use of this
invention that demonstrate the effectiveness of high-
20   power LEDs when used at an appropriate wavelength with a
suitable photosensitizer. In these example the
photosensitizer is BPD-MA (monacid form of BPD) activated
by LEDs operating at wavelengths centered around 690 nm.

25   Example 1

        An *in vitro* study on BPD-MA-treated P815 mouse
mastocytoma cells compared the cytotoxic effects of
690 nm laser light from an APDL and light from a LED
array with a 25-nm bandwidth centered at 691 nm. The
30   P815 cells were incubated for 1 hour at 37°C in the dark
with various doses of liposome-formulated BPD-MA. After
being washed, the cells were placed in duplicate 96-well
tissue culture microtiter plates at 1×10^5 cell/well.
        Plates were exposed to 2 mW/cm^2 of light for 30
35   minutes from either the laser or the LED array, this

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corresponding to a light dose of 3.6 J/cm^2. Cytotoxicity was assessed 24 hours later using the MTT assay. The results are shown in Figure 15.

5   At a drug dose of 50 ng/ml, the cytotoxicity achieved by both light sources was 100%, indicating that with high doses of light LED sources are as efficient as laser sources at effecting maximum cell kill or impairment in photosensitized cell populations in the 30-minute exposure time used here.

10

Example 2

Male DBA/2 CR mice were implanted with M1-S (rhabdomyosarcoma) cells 10 to 12 days prior to the experiment and depilated 6-7 days later. Animals

15   carrying 5-mm diameter tumors were dosed i.v. with a single dose of liposome-formulated BPD-MA (2.0 mg/kg). The mice were rested for 3 hours in the dark before exposure to light.

Irradiation was carried out using either an

20   APDL tuned to 690 nm, or an LED array with a 25-nm bandwidth centered at 696 nm. A circular area around the tumor site, 1.0 cm in diameter, was exposed to light at a power density of 110 mW/cm^2. Animals were observed for tumor recurrence over a 20-day period post-exposure. The

25   anti-tumor efficacy data is presented in Figure 16: At day 7, 100% of the mice exposed to LED light were tumor free; at day 14, 40% were tumor free; at day 20, 20% were tumor free. These curves show that a significant anti-tumor effect was obtained *in vivo* with the LED array and

30   the laser under identical treatment regimes.

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Claims

1.   A system for activating a photosensitizer
for *in vivo* or *in vitro* PDT, comprising at least one
array of light-emitting diodes and first control means
5   for operating said light-emitting diodes at a
predetermined power level and duration to activate said
photosensitizer.

2.   A system according to claim 1, wherein
10   said array comprising an array of selectively
controllable light-emitting diodes and said first control
means including means for selectively operating said
light-emitting diodes at a predetermined power level and
duration to activate said photosensitizer.

15

3.   A system according to claim 1, further
including a plurality of arrays of light emitting diodes,
each said array emitting light of different wavelength to
match the absorption spectrum of the selected
20   photosensitizer, and means for exchangeably mounting a
selected one of said arrays of light emitting diodes,
said first control means including means for activating
said selected array of light-emitting diodes for a
desired time period and intensity to activate said
25   photosensitizer for the required tissue penetration.

4.   A system according to claim 2, said array
of light-emitting diodes including diodes emitting light
of different wavelength, said first control means
30   including means for activating light-emitting diodes of a
desired wavelength to match the absorption band of the
photosensitizer that is being activated, and the required
tissue penetration.

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5.   A system according to claim 1, wherein
said first control means operates said light-emitting
diodes selectively in a pulsed mode or a continuous mode.

5

6.   A system according to claim 1, wherein a
single band of wavelengths is used to activate the
photosensitizer.

10

7.   A system according to claim 1, further
including a plurality of arrays of light emitting diodes,
said arrays emitting light of different wavelength to
match the absorption spectrum of the selected

15   photosensitizer, and a plurality of means for
exchangeably mounting selected ones of said arrays of
light emitting diodes,
said first control means including means for activating
said selected arrays of light-emitting diodes for a

20   desired time period and intensity to activate said
photosensitizer for the required tissue penetration.

8.   A system according to claim 7, wherein
said first control means controls a plurality of said

25   arrays of light-emitting diodes such that said controlled
arrays of light-emitting diodes produce high intensities
suitable for PDT.

9.   A system according to claim 1, wherein

30   said arrays of light-emitting diodes are mounted on a
flexible circuit board that permits a uniform light dose
to be delivered to non-flat surfaces.

10.   A system according to claim 1, wherein

35   said arrays of light-emitting diodes are mounted on a

curved circuit board that permits a uniform light dose to
be delivered to non-flat surfaces.

5   11.   A system according to claim 1, further
including a photodetector for monitoring the power
density emitted by said array of light emitting diodes;
said photodetector providing an output signal to said
first control means;
said first control means including second control means
10   for controlling said array of light emitting diodes in
response to said output signal of said photodetector to
keep the power density stable by compensating for any
fluctuations in the output value by increasing or
decreasing the electrical current supplied to the LEDs.
15

       12.   A system according to claim 1, wherein
said first control means further including input means
- for receiving an external control signal,
said external control signal providing control
20   information for controlling light density and duration
defining the light dose to be delivered to said tissue,
and information for terminating said light dose in
response to a detected system failure.

25   13.   A system according to claim 1, wherein
said first control means including third control means
for controlling the output power density, wavelength and
temperature of said light-emitting diodes thereby fine-
tuning said light-emitting diodes to the optimum levels
30   for activating a given photosensitizer.

       14.   A system according to claim 1, wherein the
photosensitizer used is BPD.

35

15. A system according to claim 1, wherein the photosensitizer used is PHOTOFRIN®.

16. A method of *in vivo* activation of an administered photosensitizing compound, which method comprises the step of irradiating tissues of interest with light from an LED system, said tissues having accumulated some of said photosensitizer prior to said irradiation.

17. A method of activating a photosensitizing compound, which method comprises administering a photosensitizer and subsequently irradiating an extracorporeal sample with light from an LED system.

18. The method of claim 16, wherein the photosensitizer is PHOTOFRIN®.

19. The method of claim 16, wherein the photosensitizer is BPD.

20. The method of claim 17, wherein the photosensitizer is PHOTOFRIN®.

21. The method of claim 17, wherein the photosensitizer is BPD.

1.   An apparatus for activating a photosensitizing
drug during photodynamic therapy at a single wavelength
band, the photosensitizing drug having an active-wavelength
absorption band, the active wavelength absorption band
5   encompassing the single wavelength band, comprising:
        an array of light-emitting photodiodes configured
to have a generally uniform power density between 110 and
250 mW/cm^2 over an area of at least 20 cm^2, each one
photodiode outputting light within a common wavelength band
10   centered at a predetermined wavelength, the common
wavelength band defining said single wavelength band and
spanning approximately 20 to 30 nm;
        means for stabilizing the power output of the
array; and
15   means for operating said array for an
automatically determined exposure time; and
        wherein said area is exposed to the light during
said exposure time, the light activating the
photosensitizing drug.
20

    2.   The apparatus of claim 1 in which the common
wavelength band is centered at approximately 690 nm.

    3.   The apparatus of claim 1 in which the common
25   wavelength band is centered at approximately 630 nm.

    4.   The apparatus of claim 1 in which the generally
uniform power density between 110 and 250 mW/cm^2 is
achieved by supplying a current signal to said each one
30   photodiode ranging between approximately 30 and 85 mA. .

    5.   The apparatus of claim 1, in which the
stabilizing means comprises:
        a photodetector for monitoring output light power
35   of the array of light-emitting diodes, the photodetector
generating an output signal based upon to the monitored
output light power; and
        means for adjusting electrical power input to the

array of light-emitting diodes in response to fluctuations in the photodetector output signal.

6.   The apparatus of claim 1, in which the exposure time is approximately 30 minutes or less.

7.   The apparatus of claim 1, in which the operating means comprises:
        means for monitoring the light dose delivered to said area; and
        means for discontinuing output from the array of light-emitting diodes when a desired dose has been delivered to said area.

8.   The apparatus of claim 1, in which the operating means comprises:
        means for monitoring therapeutic effect at said area; and
        means for discontinuing output from the array of light-emitting diodes when a desired therapeutic effect has been achieved.

9. The apparatus of claim 1, wherein the array of light-emitting diodes is mounted on a flexible circuit board shaped to enable delivery of a uniform dose of light to a non-flat surface.

10. The apparatus of claim 1, wherein the array of light-emitting diodes is mounted on a curved circuit board shaped to enable delivery of a uniform dose of light to a non-flat surface.

11. The apparatus of claim 1 in which the operating means controls the light-emitting diodes to operate in either one of a pulsed mode or continuous mode.

12. The apparatus of claim 1, wherein the photosensitizing drug is BPD.

13. The apparatus of claim 1, wherein the photosensitizing drug is PHOTOFRIN.

14. An apparatus for activating a photosensitizing drug during photodynamic therapy at a single wavelength band, the photosensitizing drug having an active-wavelength absorption band, the active wavelength absorption band encompassing the single wavelength band, comprising:

an array of light-emitting photodiodes configured to have a generally uniform power density between 10 and 250 mW/cm^2 over an area of at least 20 cm^2, each one photodiode outputting light within a common wavelength band centered at a predetermined wavelength, the common wavelength band defining said single wavelength band and spanning approximately 20 to 30 nm;

means for stabilizing the power output of the array; and

means for operating said array for an automatically determined exposure time; and

wherein said area is exposed to the light during said exposure time, the light activating the photosensitizing drug.

15. The apparatus of claim 14 in which the common wavelength band is centered at approximately 690 nm.

16. The apparatus of claim 14 in which the common wavelength band is centered at approximately 630 nm.

17. The apparatus of claim 14, in which the stabilizing means comprises:

a photodetector for monitoring output light power of the array of light-emitting diodes, the photodetector generating an output signal based upon to the monitored output light power; and

means for adjusting electrical power input to the array of light-emitting diodes in response to fluctuations in the photodetector output signal.

18. The apparatus of claim 14, in which the operating means comprises:

means for monitoring the light dose delivered to said area; and

means for discontinuing output from the array of light-emitting diodes when a desired dose has been delivered to said area.

19. The apparatus of claim 14, in which the operating means comprises:

means for monitoring therapeutic effect at said area; and

means for discontinuing output from the array of light-emitting diodes when a desired therapeutic effect has been achieved.

20. An apparatus for activating a photosensitizing drug during photodynamic therapy at a single wavelength band, the photosensitizing drug having an active-wavelength absorption band, the active wavelength absorption band encompassing the single wavelength band, comprising:

an array of light-emitting photodiodes configured to have a generally uniform power density between 10 and 250 mW/cm^2 over an area of at least 20 cm^2, each one photodiode outputting light within a common wavelength band centered at a predetermined wavelength, the common wavelength band defining said single wavelength band and spanning approximately 20 to 30 nm;

means for stabilizing the power output of the array; and

means for automatically discontinuing light output when one of either a monitored output light dosage or a monitored therapeutic effect is achieved at said area; and

wherein said area is exposed to the light during said exposure time, the light activating the photosensitizing drug to achieve the desired light dosage or therapeutic effect within approximately 30 minutes.

21. The apparatus of claim 20 in which the common
wavelength band is centered at approximately 690 nm.

22. The apparatus of claim 20 in which the common
5 wavelength band is centered at approximately 630 nm.

23. The apparatus of claim 20, in which the
stabilizing means comprises:
a photodetector for monitoring output light power
10 of the array of light-emitting diodes, the photodetector
generating an output signal based upon to the monitored
output light power; and
means for adjusting electrical power input to the
array of light-emitting diodes in response to fluctuations
15 in the photodetector output signal.

24. A method for activating a photosensitizing drug
at a treatment area during photodynamic therapy at a single
wavelength band, the photosensitizing drug having an
20 active-wavelength absorption band, the active wavelength
absorption band encompassing the single wavelength band,
the method comprising the steps of:
outputting light from an array of photodiodes
configured to have a generally uniform power density
25 between 10 and 250 mW/cm^2 over a treatment area of at least
20 cm^2, each one photodiode outputting light within a
common wavelength band centered at a predetermined
wavelength, the common wavelength band defining said single
wavelength band and spanning approximately 20 to 30 nm, the
30 light activating the photosensitizing drug to
photodynamically treat the area exposed;
monitoring output light power of the array;
adjusting power input to the array in response to
fluctuations in the monitored light power;
35 determining when one of a desired light dosage or
desired therapeutic effect has been achieved;
automatically discontinuing light output upon
determining said one of said desired dosage or effect has

been achieved; and

      wherein the output light power is sufficient to achieve the desired light dosage or therapeutic effect within approximately 30 minutes.

5
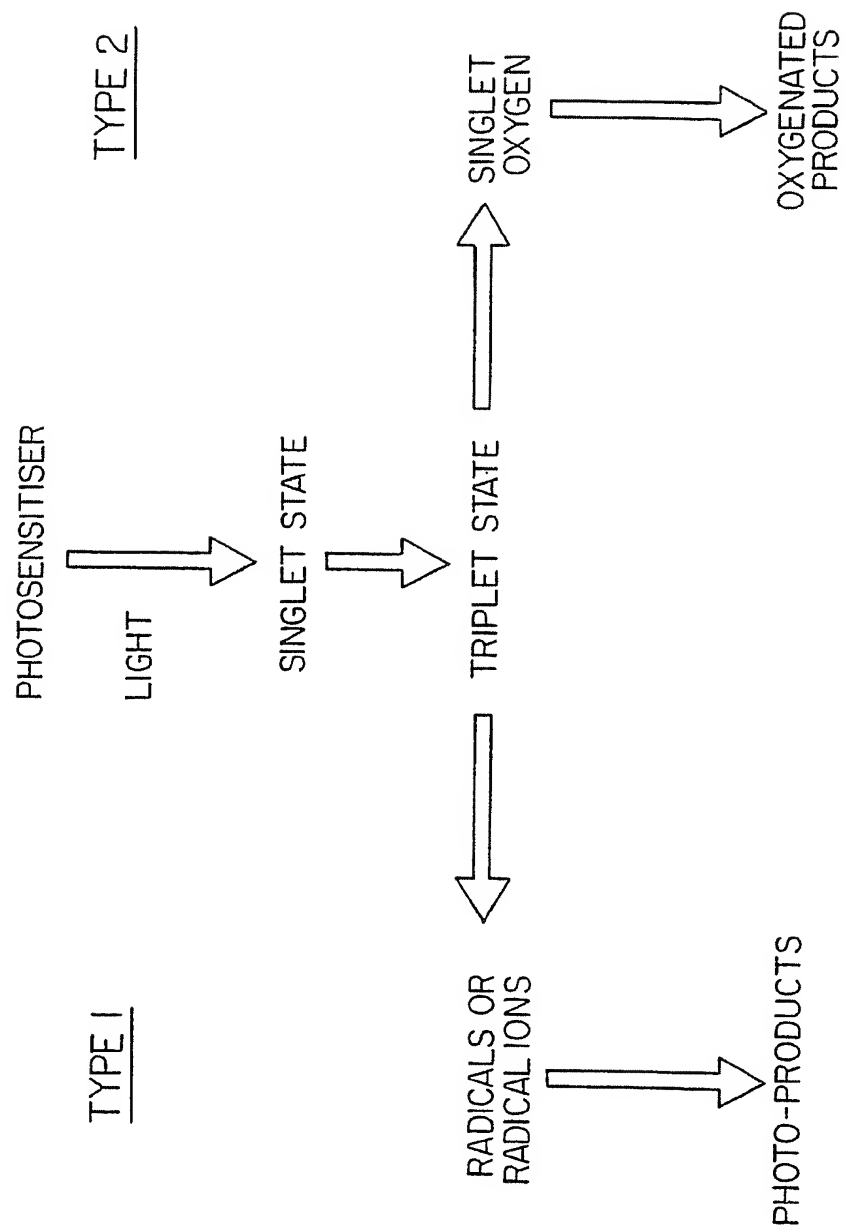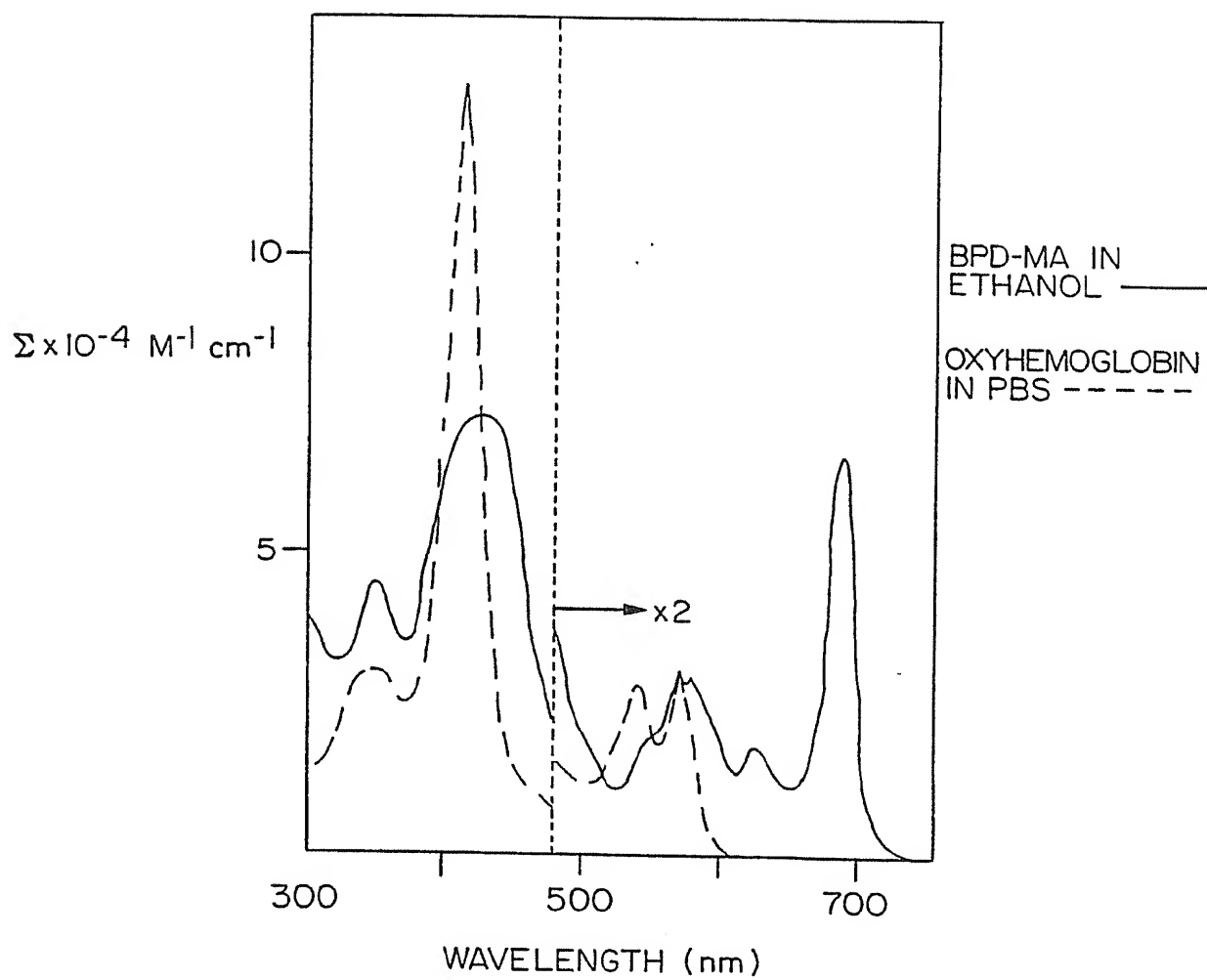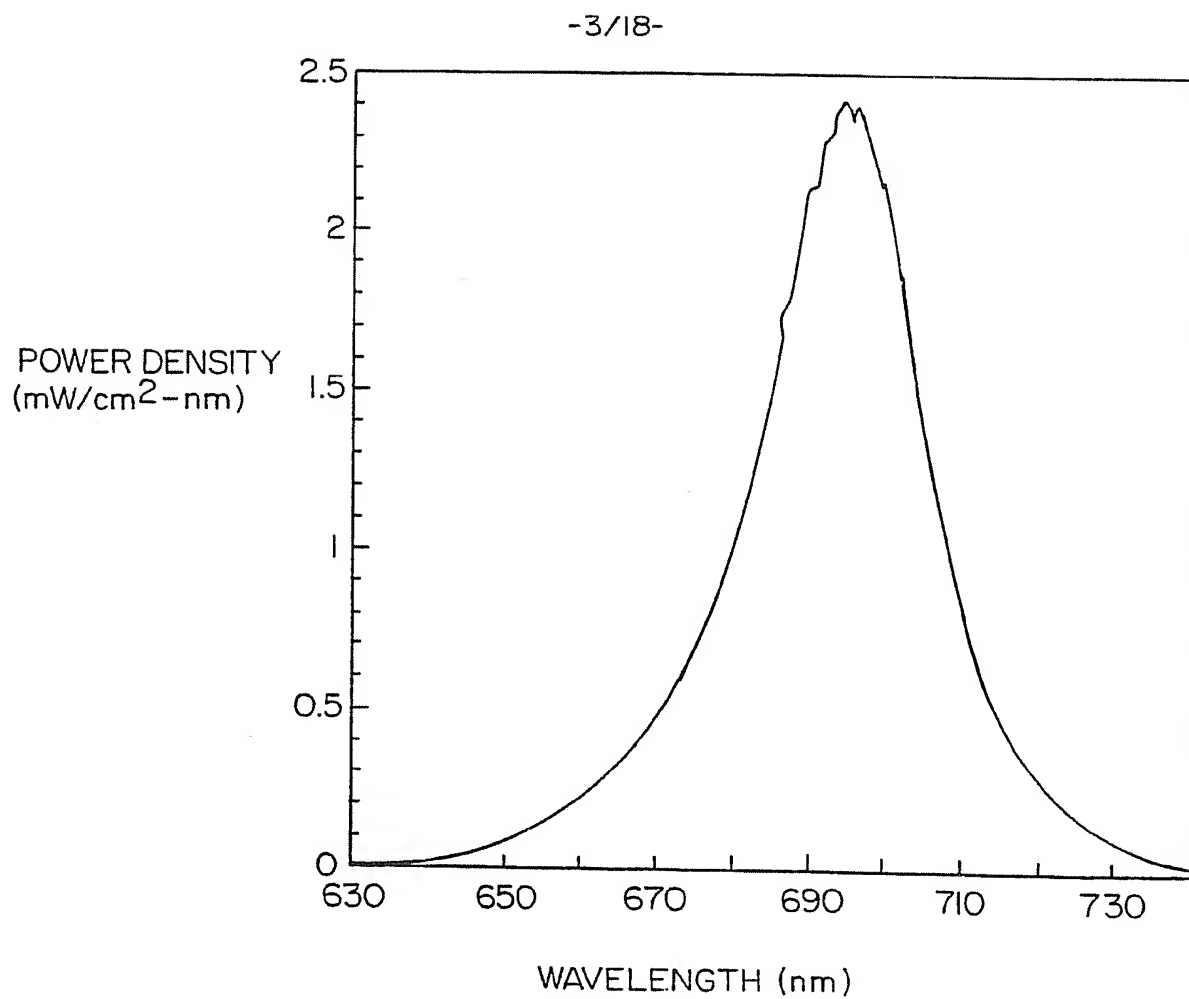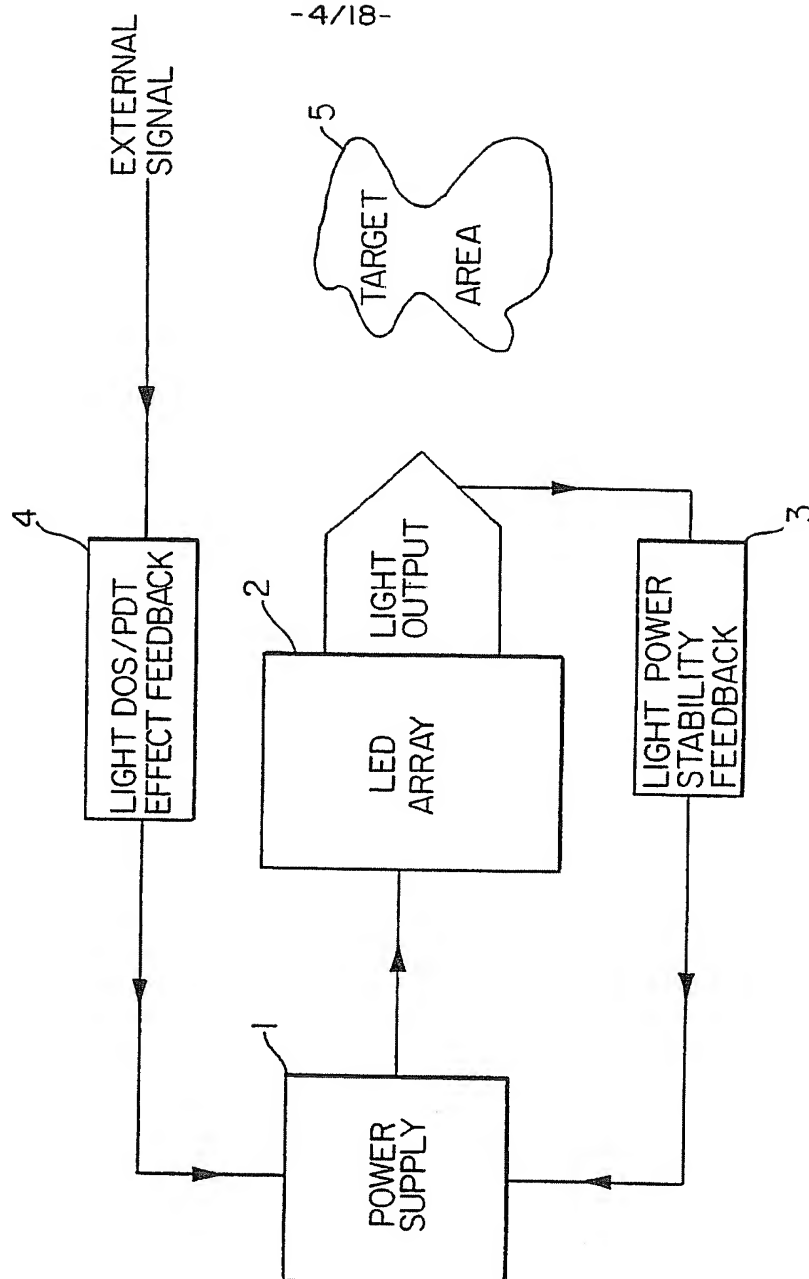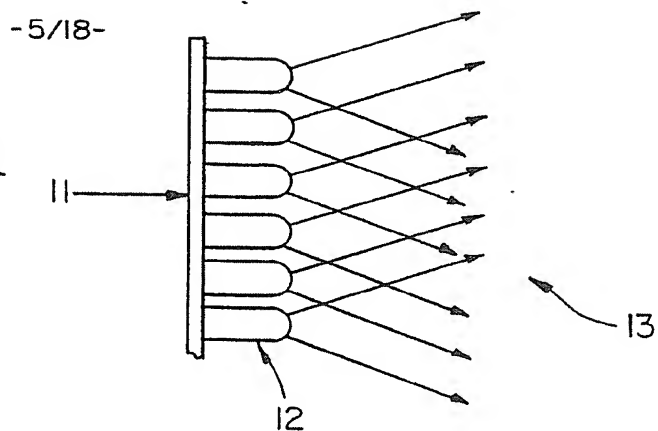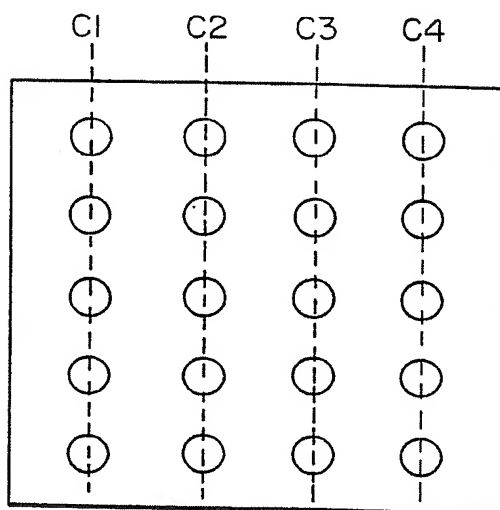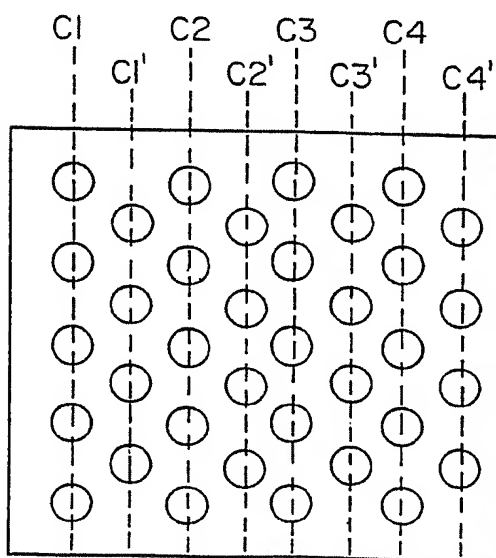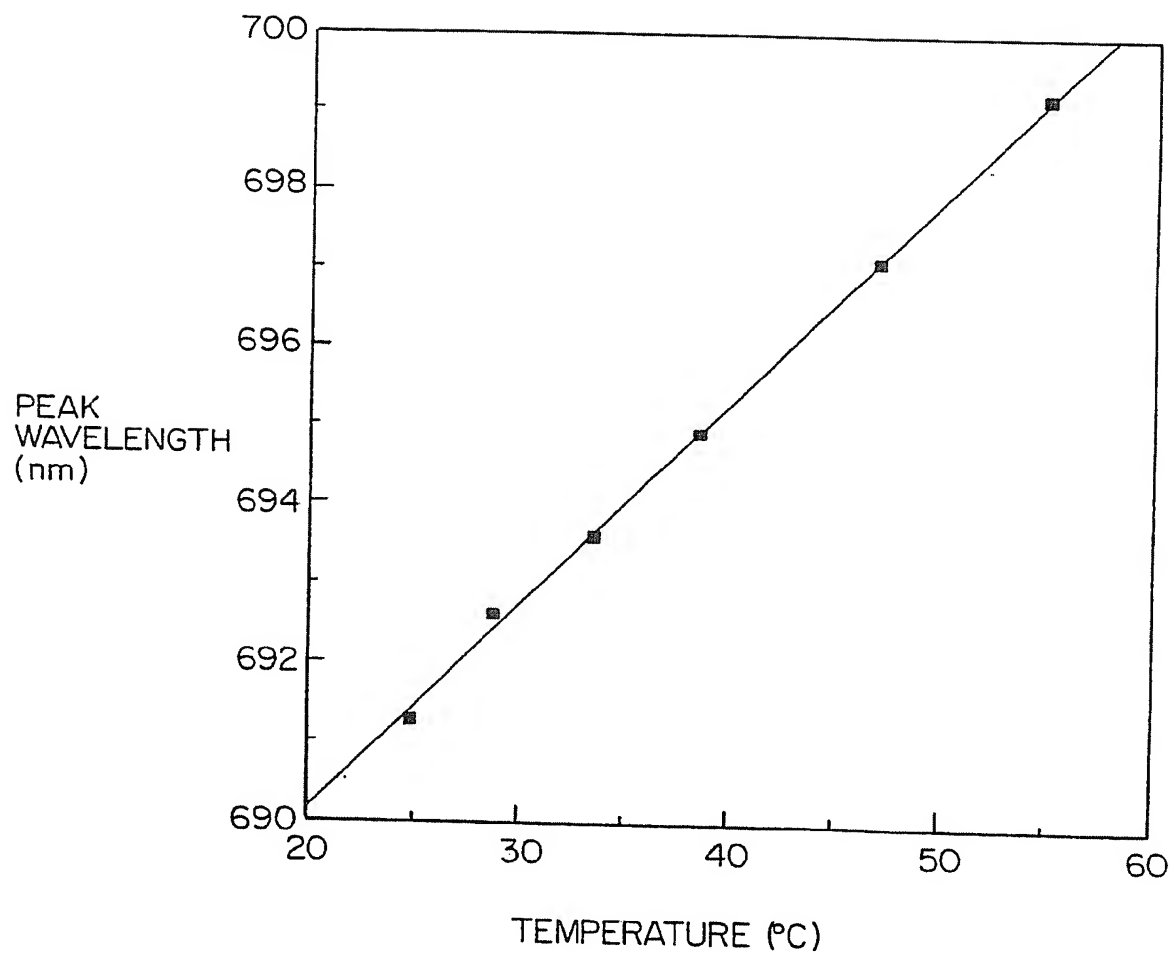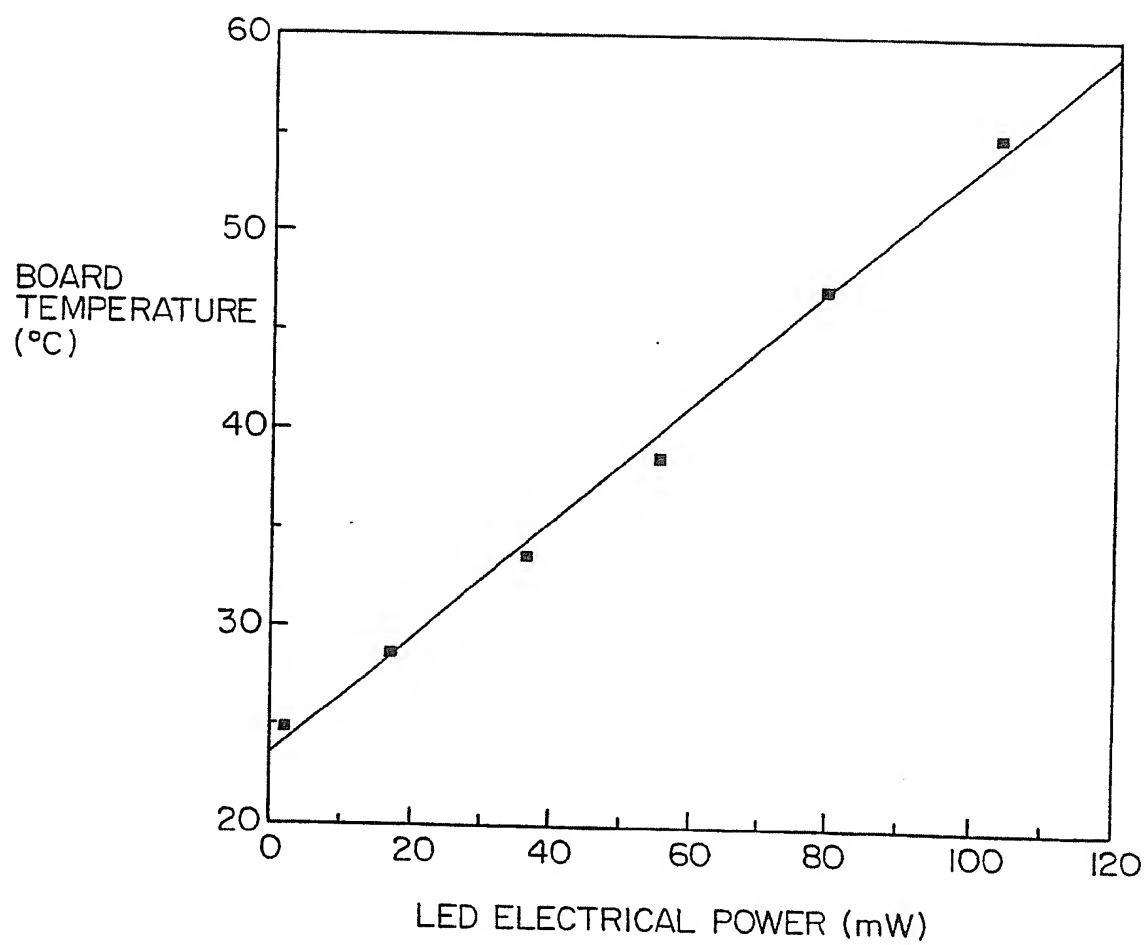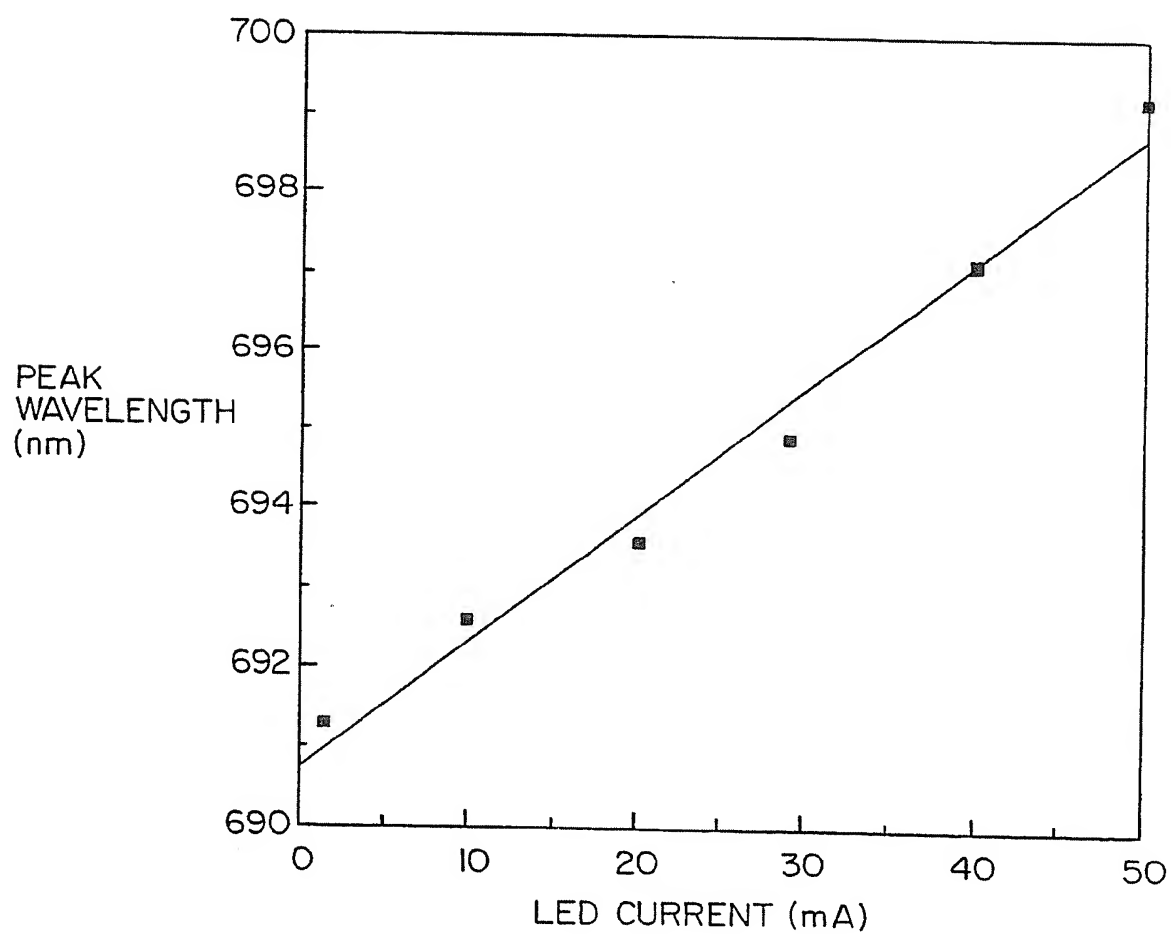
FIG. 1

FIG. 2

$\Sigma \times 10^{-4} \ M^{-1} \ cm^{-1}$

$\times 2$

BPD-MA IN
ETHANOL ———

OXYHEMOGLOBIN
IN PBS – – – –

WAVELENGTH (nm)

-3/18-

FIG. 3

-4/18-

FIG. 4

EXTERNAL
SIGNAL

LIGHT DOS/PDT
EFFECT FEEDBACK   4

TARGET

AREA   5

LIGHT OUTPUT

LED
ARRAY   2

LIGHT POWER
STABILITY
FEEDBACK   3

POWER
SUPPLY   1

FIG.5A

FIG.5B

FIG.5C

FIG. 6

FIG. 7

-8/18-

FIG. 8

FIG.9

-10/18-

FIG. 10

FIG. 11

-12/18-

FIG. 12

LIGHT
ANGLE

←—— LENS

←—— LEADS

FIG.13A

CATHODE ———

FIG.13B

FIG. 14A

22

23

23

23

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-15/18-

FIG. 14B

FIG. 14C

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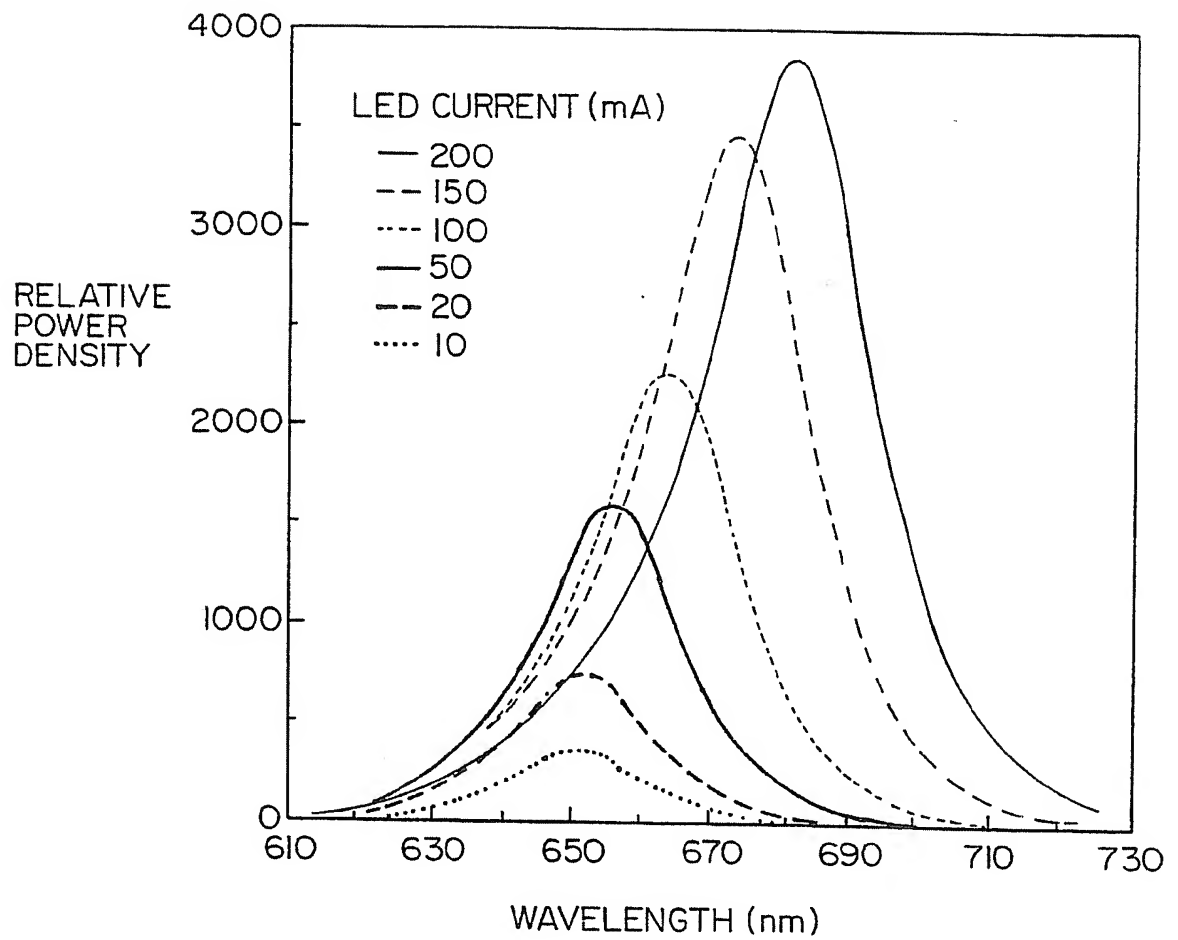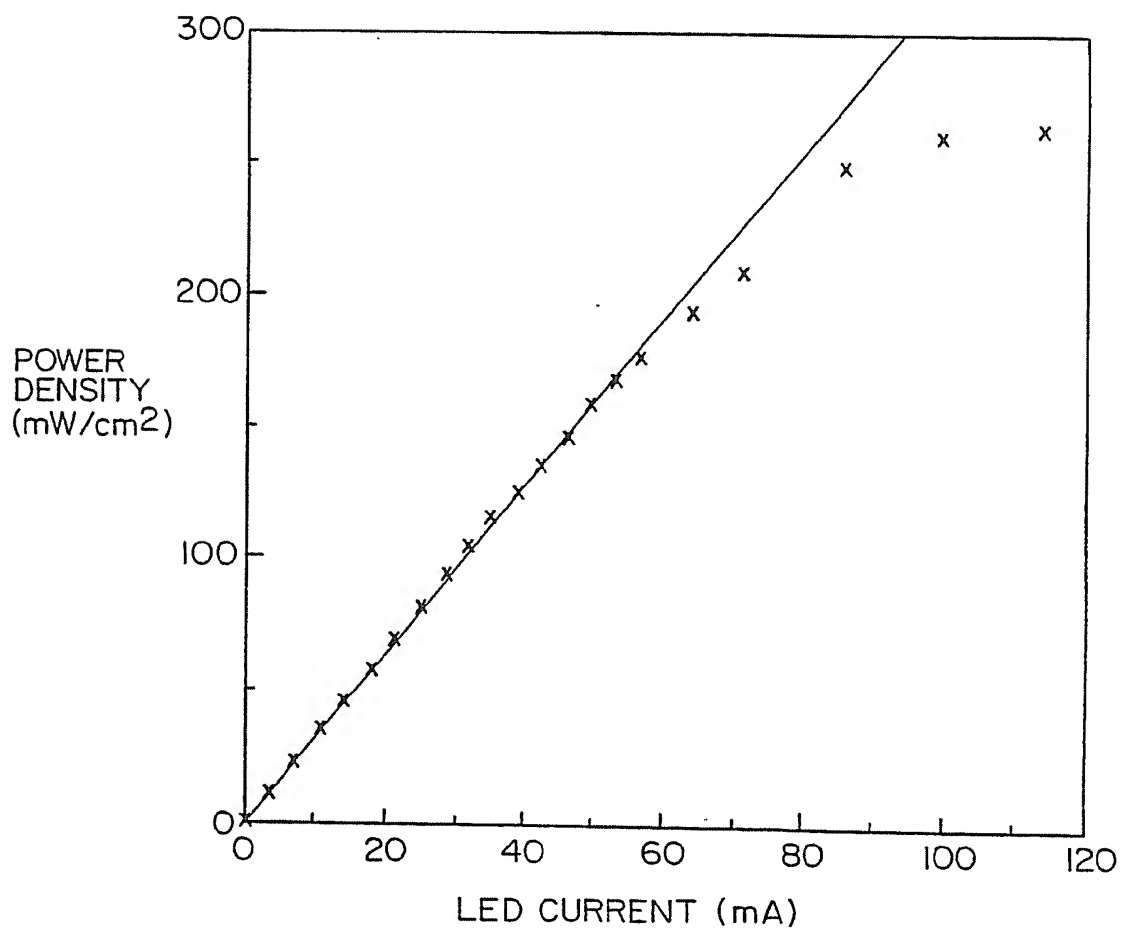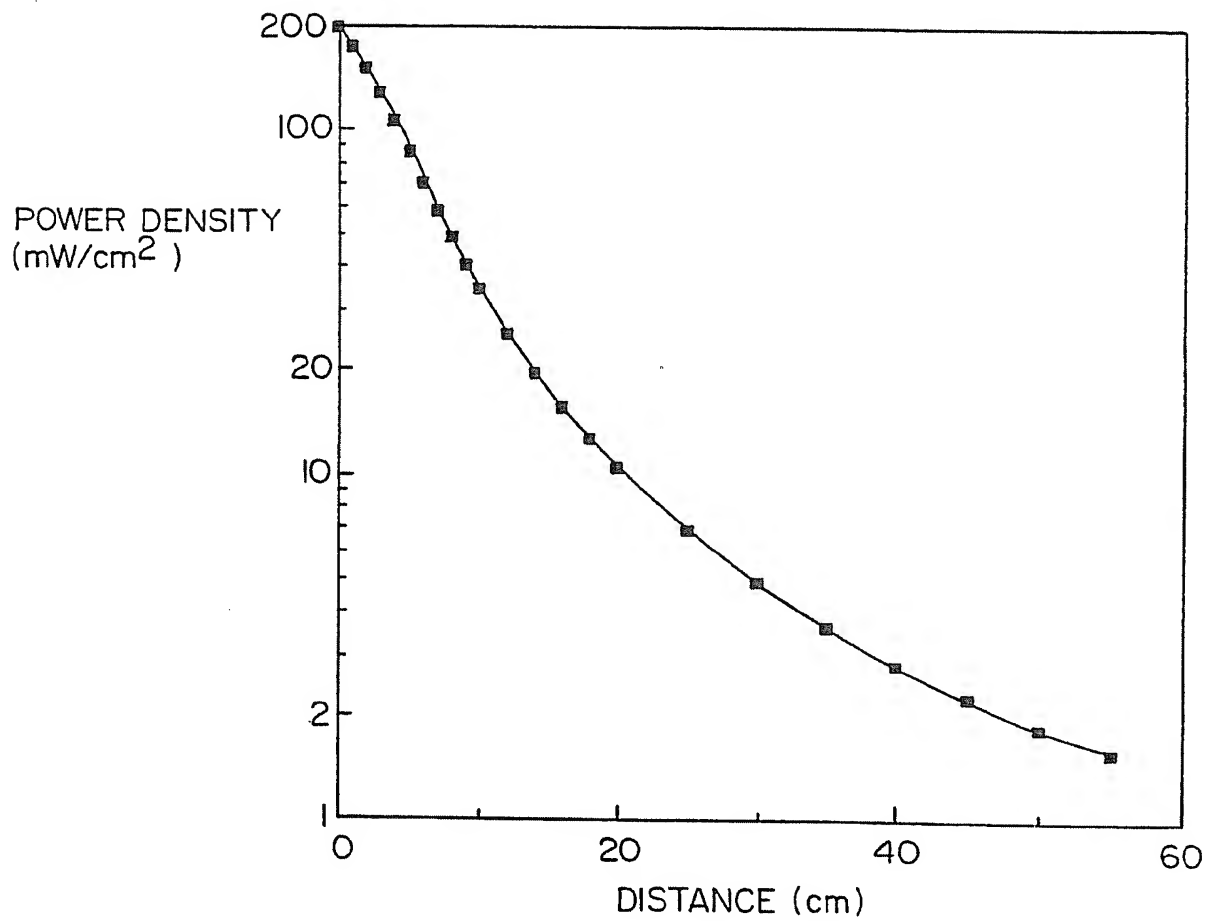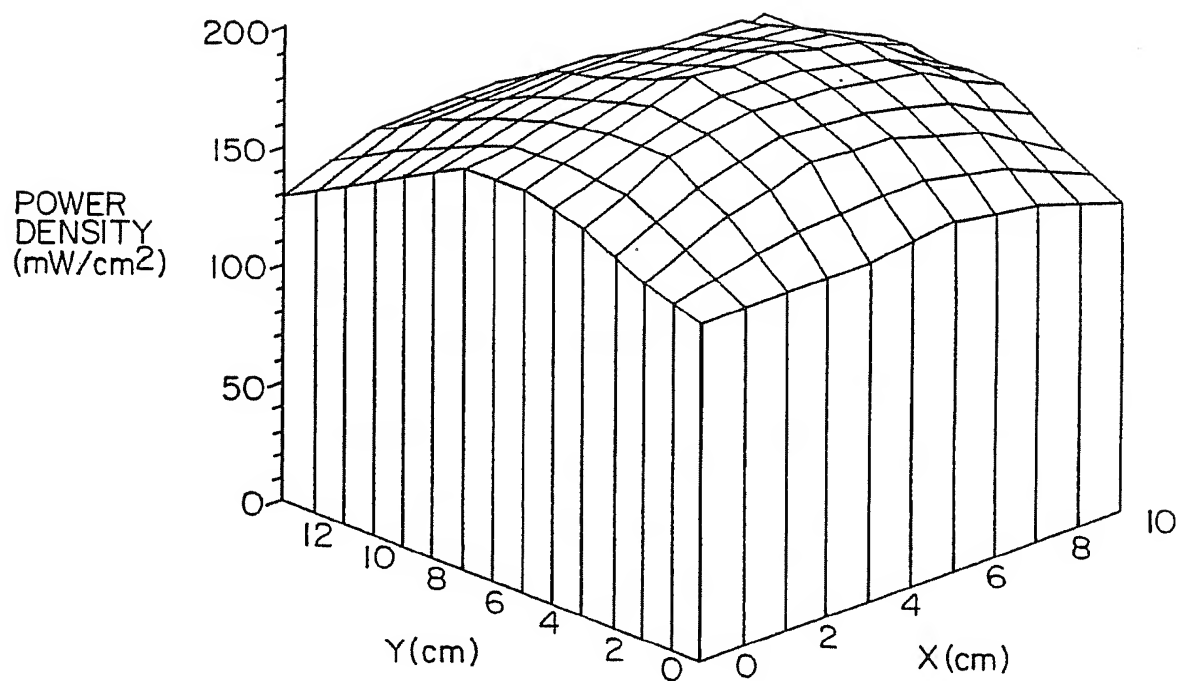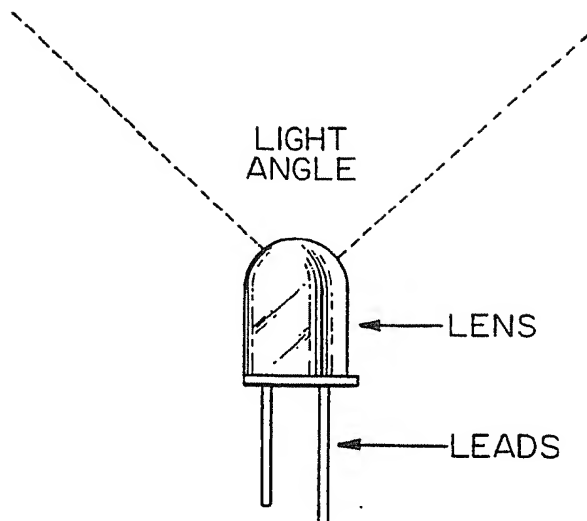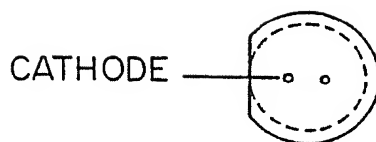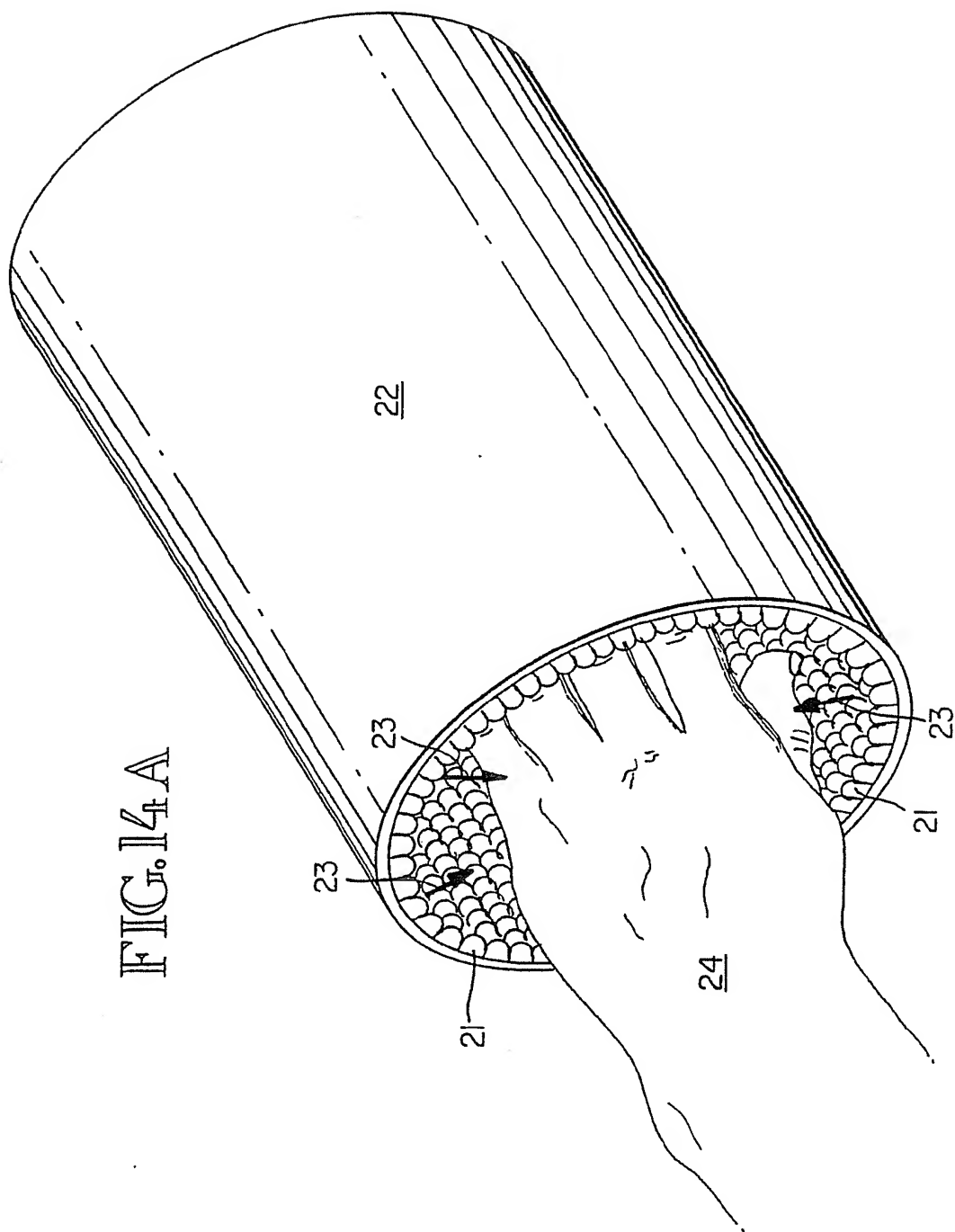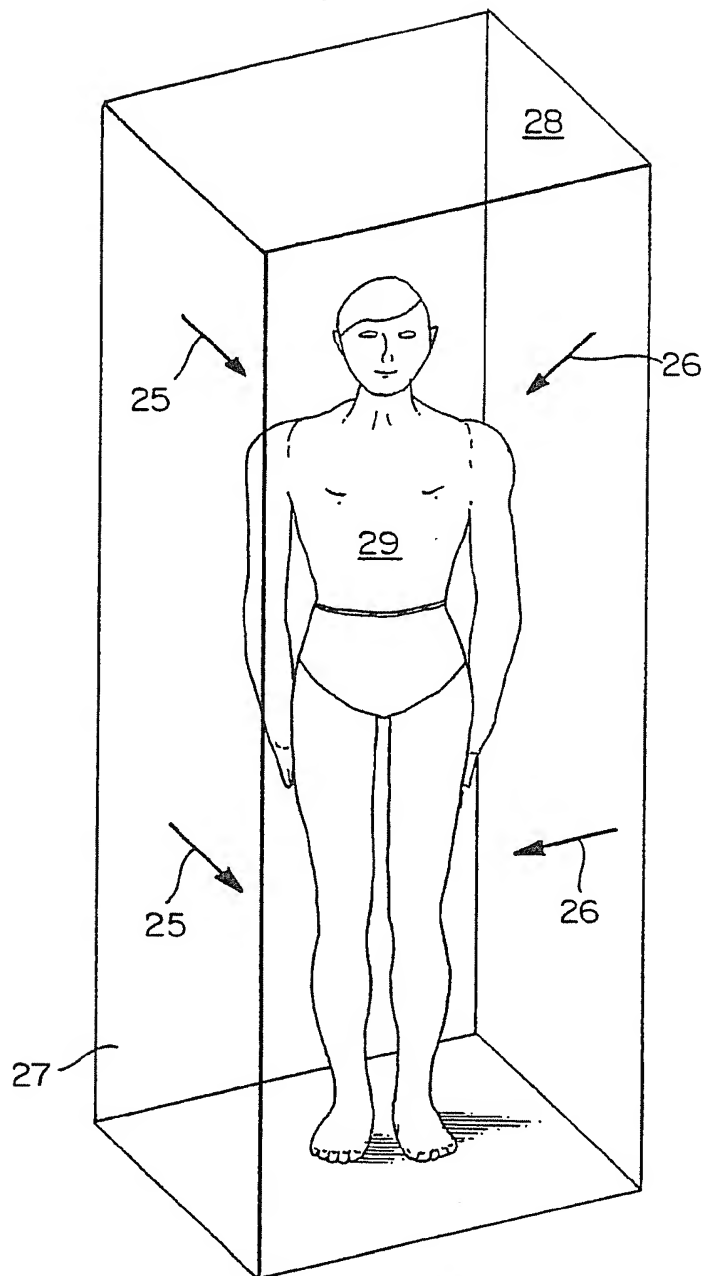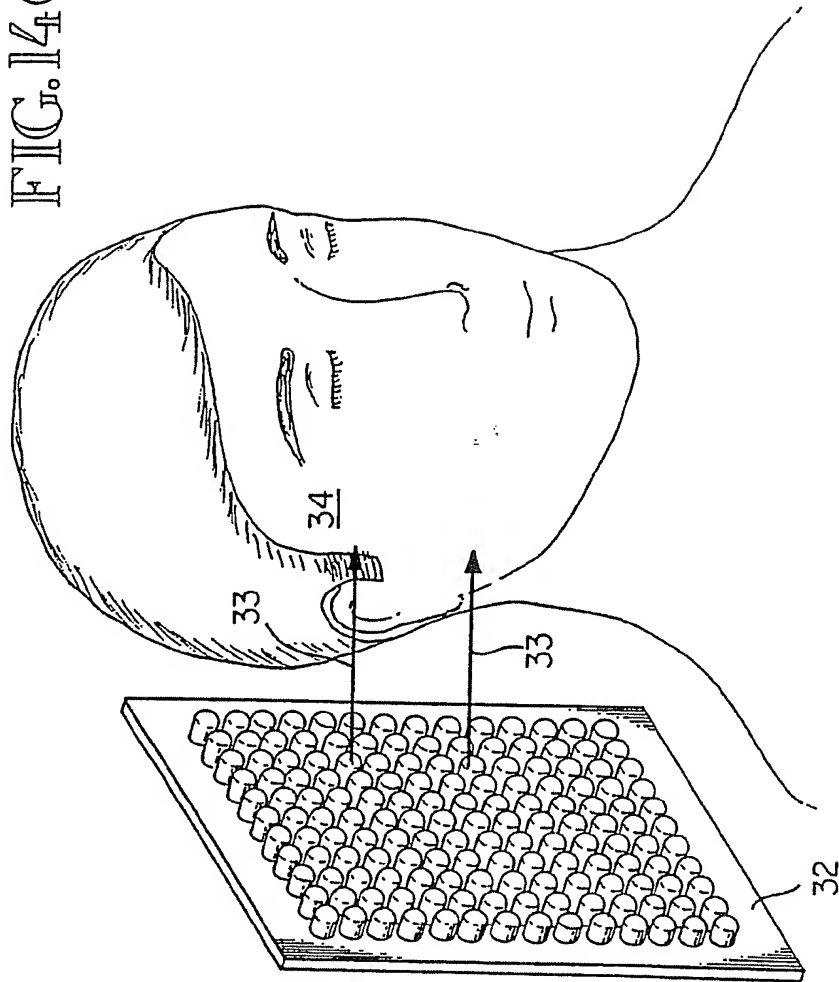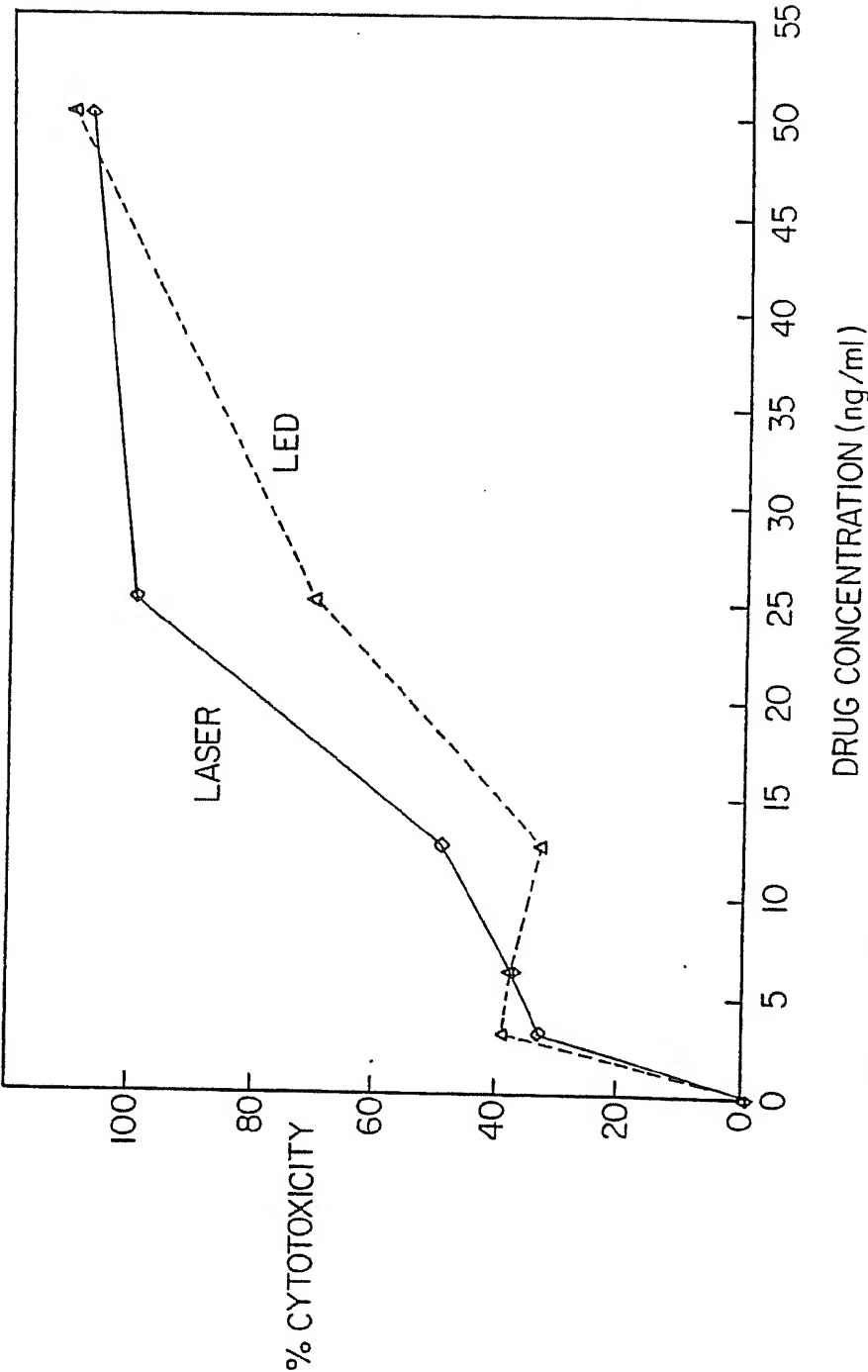
FIG. 15

FIG. 16
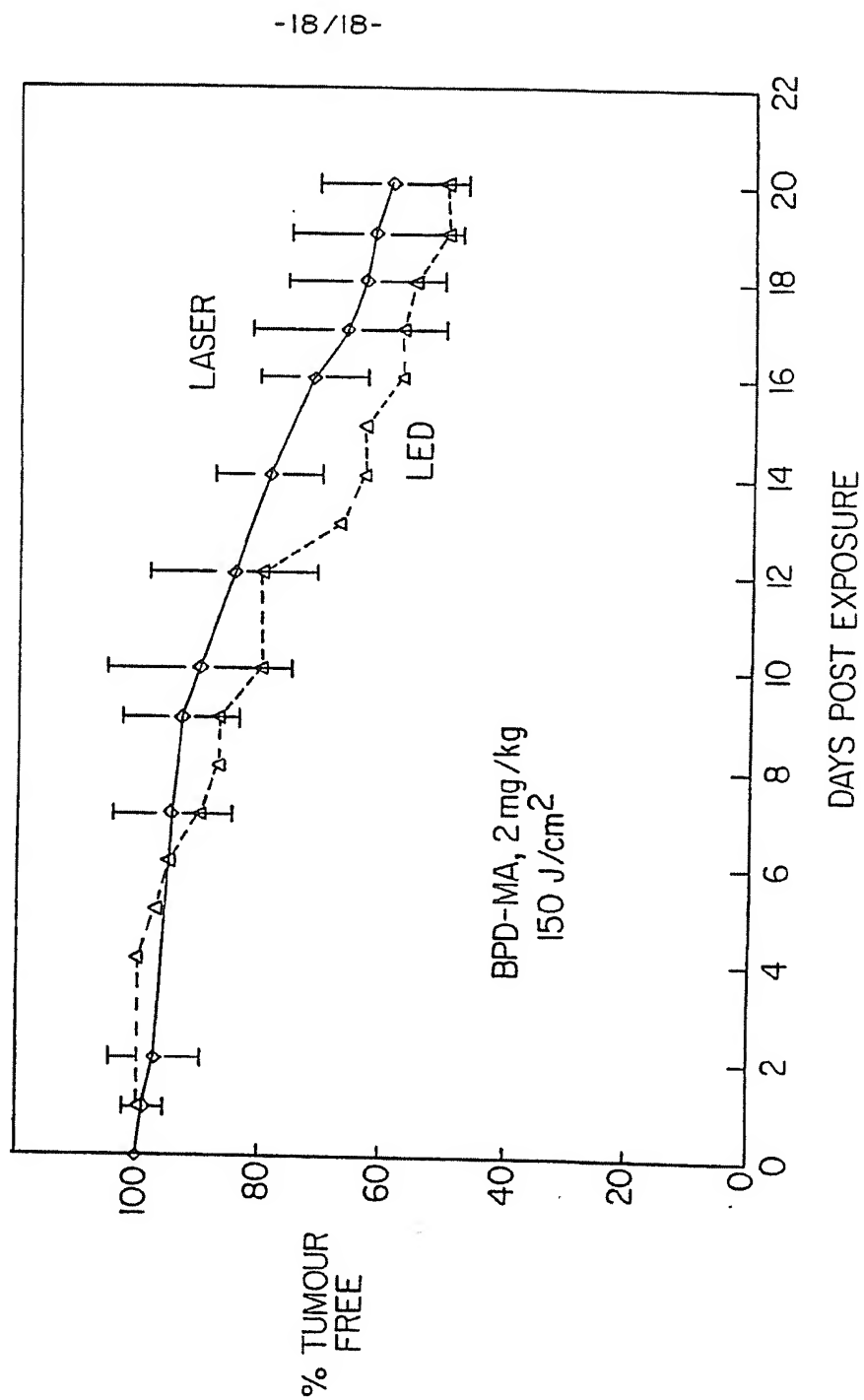
INTERNATIONAL SEARCH REPORT

A.	CLASSIFICATION OF SUBJECT MATTER

IPC(5)   :A61B 17/36
US CL   :128/396

According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/396; 128/395, 396, 397; 604/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C.	DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,822,335 (KAWAI ET AL.) 18 April 1989. See the entire document.	<u>1, 9, 10, 14, 16,</u> <u>17, 19, 21</u> 2-8, 11-13, 15, 18 & 20
Y	GB, A, 2,212,010 (LISON ET AL.) 12 July 1989. See the entire document.	2-8, 11-13 15, 18 & 20
A,P	US, A, 5,132,101 (VOGEL ET AL.) 21 July 1992.	1-21
A,P	US, A, 5,179,120 (VOGEL ET AL.) 12 January 1993.	1-21
A	US, A, 4,305,390 (SWARTZ) 15 December 1981.	1-21

[X]	Further documents are listed in the continuation of Box C.	[ ]	See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 MAY 1993	13 JUL 1993

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer *Debbie Wilcox* J. HARRISON
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-2217

Form PCT/ISA/210 (second sheet)(July 1992)

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,622,952 (GORDON) 18 November 1986.	1-21
A,P	US, A, 5,142,863 (DOUGHERTY ET AL.) 08 September 1992.	1-21
A	US, A, 4,622,953 (GORDON) 18 November 1986.	1-21
A,P	US, A, 5,163,898 (MORCOS ET AL.) 17 November 1992.	1-21
A	EP, A, 02650338 (KUREMA KAGAKU KOGYO) 04 May 1988.	1-21
A	High Technology, 30 November 1984, p. 76, Herb Brody, "Laser Light Kills Marked Tumors" page 76.	1-21
A	Cancer, Research, vol. 38, August 1978, Dougherty et al., "Photoradiation Therapy for the Treatment of Malignant Tumors", pages 2628-2635.	1-21